REMARKS

Applicants respectfully request entry of the present amendment. The amendments to the specification are made to correct editorial errors. No new matter has been added.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDMENTS

In the Specification:

Paragraph beginning at page 5, line 27:

FIG. 1C is a front view of a miniaturized mobile detector module in an exemplary UV version attached to the base of the CE system of Figs. 1A and 1B;

Paragraph beginning at page 6, line 1:

FIG. 4 is a partial top view of the CE system of Fig. 1A and 1B showing an exemplary miniaturized detector movement boundary 27;

Paragraph beginning at page 6, line 3:

FIG. 5 is a partial top view of the CE system of Fig. 1A and 1B showing an exemplary pipette movement boundary 29;

Paragraph beginning at page 7, line 5:

FIG. 19 is a partial view of the Detail B of Fig. ~~17~~18, which shows the angular placement of the fiber optic cable with respect to the capillary, which also depicts the hole and relief made in cartridge to reduce the background energy of the laser light source to the photomultiplier tube (PMT) assembly;

Paragraph beginning at page 7, line 10:

FIG. 20A is a ~~right~~ left side view of the LIF detector module of Fig. 15;

Paragraph beginning at page 7, line 12:

FIG. 20B is a ~~left~~ right side view of the LIF detector module of Fig. 15;

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Paragraph beginning at page 8, line 15:

A high throughput CE system according to the invention is shown generally in Figs. 1A-5. The system 10 includes a base 20 upon which an array of microtiter plates 22 is arranged. Into each of the microtiter plates 22, a plurality of vials or wells are molded, for example, from polypropylene or polystyrene, in which target molecules and sample molecules or molecular ligands are contained for use during an analysis, as known in the art. Alternatively, specialized microtiter plates may include one or more insertable vials. A detector docking station 24 is provided on the base 20 along one side of the microtiter plate array. A plurality of the moveable detector modules 26 is dockable at the docking station. Each detector module 26 includes a suitable detector, such as an ultraviolet absorbance detector or a laser induced fluorescence detector. Other types of detectors may be provided on the detector modules, for example, visible light absorbance, fluorescence polarization, conductivity, radioactive, and electrochemical detection.

Paragraph beginning at page 10, line 16:

The pick-up assembly 34 includes a mechanism 41 for retaining or lifting a detector module 26. In the embodiment shown in Fig. ~~2B~~2C, the retaining mechanism includes a pair of pneumatically operable piston 38 and cylinder rods 39 having magnetic solenoids 40 fixed at their ends. The magnetic solenoids 40 contact and attach to a magnetizable element disposed on each of the detector modules 26 for the purpose of magnetic lifting. The magnetizable element may be a magnetizable plate, which may be metal such as a steel. Any other suitable retaining mechanism may be provided.

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Paragraph beginning at page 10, line 32:

In general, each detector module 26 has a capillary 108/109 (*see* Figs. 6-8) extending from an inlet end 114 to an outlet end 116 of the detector module 26. The capillary includes an inlet end 108 that protrudes from the inlet end 114 of the detector module and an outlet end 109 that protrudes from the outlet end 116 of the detector module. The detector modules comprise an upper housing 104 and a removable cartridge component 102 that can be removed when the capillary needs replacing and so that a fresh cartridge component with a fresh capillary can be maintained in reserve and quickly replaced in a detector module. The capillary is laid in an appropriately sized channel 121 formed in an upper surface of the cartridge component and a corresponding channel formed in the lower surface of an upper housing of the detector. A first electrode 110 is provided at the inlet end 114 of each detector module, and a second electrode 111 is provided at the outlet end 116 of each detector module. The capillary inlet 108 and associated electrode 110 are located substantially together such that both may be inserted in a single well on the microtiter plate array 22. Similarly, the capillary outlet end 109 and associated electrode 111 are located substantially together such that both may be inserted in a single well on the microtiter plate array 22.

Paragraph beginning at page 11, line 21:

Each detector module includes a desired detector assembly such as a UV detector 100 (as shown in Fig. 7A), discussed further below. A window 123 is formed in the capillary 108 such that the window 123 is aligned with the desired detector for sample

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separation detection. The window, approximately 8 mm in length, is formed in an external polyimide coating on a fused silica capillary using a suitable tool by mechanically removing a strip of the external polyimide coating from the outside of the fused silica tube. Exemplary capillaries are made from narrow diameter fused silica tubing of various inside and outside diameter configurations. The polyimide coating is added to make the normally brittle fused silica somewhat flexible to provide for normal handling and installation procedures. Other types of capillaries are commercially available. Depending on the type of assay required, other means of providing a window on the capillary may be used such as laser ablation and hot sulfuric acid processes, as known in the art.

Paragraph beginning at page 18, line 1:

In certain cases, sample preparation may involve more than just a simple dilution operation. For example, if a competitive ligand is being used to develop a competitive assay, then some incubation time delay is probably required after the addition of the sample to the existing target/ligand mixture complex. After a sample mixture is prepared, in certain cases, a relatively short incubation time of a few seconds to a few minutes is required to allow competitive reactions among the sample components to reach equilibrium. After equilibrium has been achieved, but before excessive incubation time results in inconsistent assay results, the CE injection is made and the analytical separation is performed. Accurate reproducibility of the incubation time, defined as the point of addition of the sample or ligand to the point the complex is removed from the equilibrium solution by the injection event is critical to recognizing affinity effects

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through comparison with negative control injections. The CE system of the invention can repeat this interval with a variation of less than .5 seconds ~~in~~ among one-minute ~~incubation~~incubations.

Paragraph beginning at page 19, line 8:

When the capillary is sufficiently rinsed with dilute sample solution, the solenoid valve controlling the 10 psi rinsing pressure is turned off and the Z-axis arm picks up the detector module from the working plates, the lifting mechanism still being energized. Once raised, the detector module is transported to a vial containing pure buffer solution and the inlet electrode/capillary pair is dipped into the solution by the Z-axis to remove traces of sample contaminating the external surfaces of the inlet electrode/capillary pair. After dipping, the detector module is raised, translated, and dropped again into an empty vial to catch waste buffer clinging to the surfaces of the inlet electrode capillary. Any liquid attached to the pair is blown off into the empty vial by turning on the 10 psi air normally used to create rinsing pressure in a sealed container. Since in this case, the O-ring is not brought in contact with the top of the waste vial, the air flows fairly vigorously and blows off any clinging liquid. Now the detector module having a decontaminated and dry inlet capillary/electrode is raised, translated and lowered into a sealable vial containing a solution of target molecules. The Z-arm applies pressure to the top of the vial once again, and the system turns on a solenoid valve controlling the pressure used for sample injection. When the interior of the target vial is pressurized (typically 0.5 psi for 5 sec with a 50 μm inner diameter capillary), sample is injected (typically 50 nL) up into the very beginning of the inlet capillary end. Now the Z-

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axis arm again lifts the detector module and returns it to the same two working plate wells containing the sample rinsed through the capillary. The lifting mechanism is released from the detector module and the arm assembly 12 is free to go begin another sample preparation step or go to move another detector module 26. ~~After completion of the analysis and discharge, the detector module 26 is then picked up by the arm assembly 12 to be returned to the docking station 24.~~ Simultaneously, the high voltage is turned on and the target begins its migration to the outlet working plate well, passing through a solution containing potential ligands. Any interaction between the diluted sample buffer and the target injection liquid will cause the resulting electropherogram to deviate from the control profile where there is no potential ligand material present. At the completion of the programmed electropherogram run time, the detector module is recovered by the lifting mechanism and transferred back to the docking station where the hold-down mechanism squeezes the inlet o-ring between the underside of the detector and the top of a 4 mL buffer vial. A full vial at the outlet end of the detector washes off the outlet electrode/capillary end and catches flow coming from the capillary during the buffer rinsing operation. Now the rinsing pressure, typically 10 psi, is again turned on and a couple hundred microliters of pure buffer are rinsed through the capillary from inlet to outlet end to remove all traces of the previous sample and the target. The detector module is now available to have the next sample dilution solution rinsed through the capillary.

Paragraph beginning at page 21, line 16:

Appropriate passages are available for extending an inlet capillary end 108, an inlet electrode 110, an outlet capillary end

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109, and an outlet electrode 111 at the ends of the cartridge 102, with an extension of about 2.0 cm to reach near the bottom of a sample and a discharge well. The cartridge 102 has at both ends passages 140 for receiving the capillary inlet and the outlet. The inlet end 114 of the detector serves to position the capillary inlet 108 with a well containing any of several liquids. The outlet end 116 of the detector serves to position the capillary outlet 109 to a well for collecting the discharge during analysis and rinsing operations. Surrounding an alignment probe feature at each end of the cartridge, is an O-ring 112 sized so as to seal with the top of any vial from which one would need to rinse or inject. This would include dock vials to rinse and to initialize the capillary for the next sample, the working plates from which sample solution is rinsed through the capillary, and the target vial from which a small injection volume is forced partway up the inlet end of the capillary. Additionally, the inlet electrode 110 and the outlet electrode 111, which are aligned and in parallel with the capillary, are also extended from each end of the cartridge 102. However, the electrodes are permanently attached and electrically connected to the upper housing 104. Specifically, the inlet electrode 110 is soldered to conductor 138 and the outlet electrode 111 is soldered to conductor 138. The two electrodes slide through specific clearance holes 140 in each end of the cartridge during removal or installation.

Paragraph beginning at page 22, line 10:

Between the magnetizable hold-down plate 106 and the cartridge 102, a custom photodiode amplifier assembly 118 is provided which connects with the power and signal cable 120 ~~from~~ mounted to the upper housing 104. The cartridge 102 also contains

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a capillary alignment channel 121 on its top center surface that runs longitudinally for holding the capillary. The cartridge 102 also contains a capillary window location 122 near the outlet end of the detector module 100 for detecting UV light variations as a sample mixture moves through the capillary window from the inlet end to the outlet end of the capillary.

Paragraph beginning at page 23, line 13:

The upper housing 104 has a first retaining latch 128 and a second retaining latch 128 on the left and right sides to tightly connect both the upper housing 104 and the cartridge 102 together. The upper housing 104 also has a magnetizable pick-up plate 130 on the top surface of the upper housing 104. The magnetizable pick-up plate 130 has a first magnetic alignment guide 132 and a second magnetic alignment guide 133 on the top side ends of the magnetizable pick-up plate 130. The magnetizable pick-up plate 130 has, at one end, a flexible cable guide connector 134 for attachment to the base of the CE system to contain the several electrical cables, the UV light source cable, and the pneumatic tubes necessary to make the detector module function. The upper housing 104 and the magnetizable pick-up plate 130 also contain corresponding passages for acceptance of various electrodes and cable guides. For example, the upper housing 104 has a power and signal cable 120 which connects through to the cartridge 102 to the custom photodiode amplifier assembly 118. The upper housing 104 also houses a fiber optic cable 136 for a UV light source and high voltage cables 138 for the electrode cable wires. Two passages are shown on the magnetic pick-up plate 130 to have access for coolant tubing to connect to a fitting 142, which

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provides for connection to passages internal to the upper housing 104 and to passages internal to the heat sink 124.

Paragraph beginning at page 28, line 9:

The cartridge 102 of the detector module includes a first end block 204 where a capillary inlet end 108 and its associated first electrode 110 extends out from the inlet end 114 of the detector module. The cartridge also provides a second end block 206 for a capillary outlet end 109 and its associated second electrode 111, which extends out from the outlet end 116 of the detector module. Various ports are made available in the cartridge through the end blocks. The end block 204 containing the inlet portion of the capillary and the electrode has a through hole 240 to accommodate a pneumatic connection 241 (Fig.24) for the rinse and inject pressure. The end block 206 containing the outlet portion of the capillary and the electrode provides a barbed connector 242 for connecting tubing for the coolant supply that flows through the cartridge. The outlet end of the detector module provides attachment for a metal support 216 (Figs. 16A and 18) for connecting the cable guides 25, which retains the cabling from various sources to prevent tangling and ease of movement of the detector modules. This metal support 216 also provides mounting for the fiber optic connector 212 (as shown in Fig. 18) used to supply excitation laser light to the optical fiber segment permanently imbedded in the cartridge with epoxy.

Paragraph beginning at page 30, line 9:

A capillary mask 416 to block background excitation light is provided above the window 123. A microscope objective lens assembly 400 is provided above the mask ~~415~~416. The objective lens

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assembly is selected for high magnification, which translates to high numerical aperture, or preferably N.A. 0.85. The higher the N.A. of an optical element, the larger is the angle over which light passes into or out of the device. In the case of the 63X objective lens 402 used in this embodiment, the N.A. calculation shows that light within a 116 degree solid angle emitted by the fluorescing liquid in the capillary will be collected by the microscope lens. The liquid in the capillary is located at a working distance away from the front lens surface of the objective so that any light emanating from the liquid exit the lens inside the objective in parallel rays. Conversely, light entering the lens from any point other than the center of the capillary will not travel in a line parallel to the axis of the objective lens assembly. These parallel light rays pass through a high-pass optical interference filter 404 that is intended to block the 488 nm excitation energy, but allow the 520 nm fluorescent energy to pass through with minimal transmission losses. This type of filter requires that light to be filtered pass through the filter on a ray 406 at virtually 90 degrees to the surface of the filter. The inside of the microscope objective is modified to accommodate and hold securely the filter in a plane 90 degrees to the axis of the objective. In this arrangement, because only light from the sample liquid travels through the objective on rays parallel to the axis, (the optimum performance angle), the 488 nm component of light from the liquid is expected to be attenuated by almost six orders of magnitude. Conversely, the 520nm light passing through the filter on a ray normal to the surface is only attenuated by about 5%. After the filter in the light path, plano-convex focusing lens 408 is disposed to create a virtual image of the capillary lumen from the parallel rays traveling through the filter a distance

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beyond the lens equal to the focal length of the lens. The virtual image is essentially a reconstruction of the capillary lumen in a plane behind the lens from the side where the parallel light enters. To further block extraneous light rays from striking the PMT sensor, a circular mask 410 is installed behind the plano-convex lens with a center hole diameter selected to allow only light rays coming from the center of the capillary to be focused through the hole. A light-blocking O-ring 112 is also disposed between the mask 410 and the detector 224. Rays from scattered light or other sources are thus not able to pass through the mask behind the lens. This optical design ~~to~~ eliminates scattered rays from striking the PMT, minimizes the level of background light and maximizes the signal-to-noise of the arrangement. Finally, the light exits the mask and passes through to the PMT sensor 414. In a further embodiment, to eliminate even more background light, a pinhole mask (not shown) is placed at the plane of the virtual image, between the circular mask and the PMT sensor. This pinhole mask must be carefully aligned, or the signal energy is clipped by the mask as well and the ratio of signal-to-noise actually drops. Accordingly, the pinhole mask may be omitted if desired.

Paragraph beginning at page 31, line 30:

The upper housing 104 holds a magnetic pick-up plate 130 on its top surface. The removable cartridge ~~104~~ 102 has passages available for the light coming from the capillary window 123 (Fig.19) to reach the PMT 224 for detection. An O-ring 112 is fitted in between the upper housing 104 and the magnetizable pick-up plate 130 to seal out any ambient light, which may leak into the PMT light sensor. A first magnetic alignment guide 132 and a second magnetic alignment guide 133 are positioned at both ends on

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top of the magnetic pick-up plate 130. The guides 132 and 133 are provided to exactly position the pick-up magnets on the Z-arm on the pick-up plate when securing a detector module for transport. Realignment of the detector module relative to the Z-arm is necessary on each manipulation to maintain the accuracy required to insert the electrode/capillary into the small well opening reliably. The PMT assembly 224 is positioned on top of the magnetic pick-up plate 130, which is aligned to the capillary window for detection. More than one PMT assembly may be attached to the LIF detector depending on the type of analysis. For example, a single capillary can be fabricated with two viewing windows such that an "early" and a "late" signal can be produced from a single analysis separation event. The early and late detector signals comparatively can be interpreted to reveal difficult-to-obtain kinetics information about the binding properties between potential therapeutic drug targets and various ligands including unknown molecules present in the extracts of natural samples, synthetic compounds, and combinatorial mixtures.

Paragraph beginning at page 32, line 23:

In Fig. ~~17~~18, a top view of the cartridge 102 reveals an angular placement of an optical fiber segment 230. Deliverance of the excitation energy by the fiber optic cable through the fiber optic connection to the X-axis of the capillary lumen at some non-90° angle (as shown in detail in Fig. 19) virtually eliminates the excitation wavelengths from the axis from which the fluorescent energy is being detected. The angle is preferably as small as possible without reaching the critical angle, at which light is reflected and does not enter the fluid in the capillary. A 45 degree angle has been found to be suitable. Eliminating the

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excitation component reduces the amount of detectable background energy and increases the signal to noise ratio of the detector. The optical fiber supplying the laser light is closely placed next to the capillary window as shown in Fig. 25.

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